

Title: A Randomized, Double-blind Study Comparing 3% Chloroprocaine versus 2 % Lidocaine/  
Epinephrine/ Bicarbonate/ Fentanyl for Epidural Anesthesia in Elective Cesarean Delivery  
PI : Nadir Sharawi, MD  
Site: University of Arkansas for Medical Sciences

**Study Title:** A Randomized, Double-blind Study Comparing 3%  
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Cesarean Delivery

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## Abbreviations

ASA	American Society of Anesthesiologist
BP	Blood Pressure
CSE	Combined Spinal Epidural
CSF	Cerebro-Spinal Fluid
ECG	Electrocardiogram
HIPAA	Health Insurance Portability and Accountability Act
L&D	Labor and Delivery
LEBF	Lidocaine, Epinephrine, Bicarbonate and Fentanyl
Mcg	Microgram
Min	Minute
ml, mls	Milliliter, Milliliters
PACU	Post Anesthesia Care Unit
T7	Thoracic Dermatome Level 7
T10	Thoracic Dermatome Level 10
T12	Thoracic Dermatome Level 12
UAMS	University of Arkansas for Medical Sciences
VAS	Visual Analogue Scale

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## **Background and Rationale**

Regional anesthesia is commonly used for elective and emergency cesarean delivery. It provides numerous safety advantages when compared to general anesthesia for both the mother and fetus<sup>1</sup>. Epidurals also have the added benefit of being able to provide pain relief throughout labor and in the event of cesarean delivery, epidural analgesia can be “extended” to provide surgical anesthesia. Numerous studies have been performed to assess the onset times of various local anesthetics when administered through an epidural catheter. Attempts to reduce anesthetic onset time and improve the quality of intraoperative analgesia have been attempted by using different local anesthetic solutions and by the addition of other drugs to the epidural solution (such as epinephrine, fentanyl and sodium bicarbonate).

A recent meta-analysis concluded that the optimum local anesthetic solution for extending a labor epidural from analgesia to surgical anesthesia has yet to be determined<sup>2</sup>. In 1994, a retrospective study compared 1.5% lidocaine/bicarbonate/epinephrine mixture to 3% chloroprocaine in parturients with pre-existing epidural catheters for urgent cesarean delivery<sup>3</sup>. It was found that the chloroprocaine group had a significantly faster onset of anesthesia compared to the lidocaine group. Both drugs provided excellent anesthesia. However a high quality study comparing 3% chloroprocaine with 2% lidocaine/ epinephrine/ bicarbonate/ fentanyl (LEBF) in terms of anesthetic onset times has yet to be performed.

Women in labor frequently request an epidural to provide pain relief. Epidural pain relief is commonly provided by the administration of a low concentration of local anesthetic and opioid solution through an epidural catheter. This solution is delivered by an automated epidural infusion pump. In the event that a cesarean delivery is required, the pre-existing epidural is frequently used to administer a higher concentration anesthetic solution to allow pain free cesarean delivery. This is commonly referred to as an “epidural top up” or as an “extension of the epidural block.”

Our standard practice at UAMS for an epidural top up is LEBF or 3% chloroprocaine. These two mixtures are routinely and almost exclusively used for epidural cesarean delivery. The decision on which mixture to use is based solely on physician preference. It is likely that the LEBF mixture is used more frequently but we consider both local anesthetic mixtures as equals and the standard of care at UAMS. We do not use any other local anesthetics (unless there are very specific reasons).

## **Specific Aims**

The aim of this study is to compare the speed of onset and anesthetic quality of our two current clinical dosing regimens (LEBF and a solution of 3% chloroprocaine) in elective

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cesarean delivery. We hypothesize that the use of a 2% lidocaine/ epinephrine/ bicarbonate/fentanyl mixture will have an equivalent onset time to surgical anesthesia as compared to 3% chloroprocaine.

### **Primary Outcome**

The primary outcome will be the onset time to surgical anesthesia, as reported by the participant using a standard procedure This will be measured by the time taken from the end of the epidural loading dose to develop a loss of touch sensation using a neurotip® (Owen Mumford, USA) device bilaterally at the T7 dermatomal level.

A blunt plastic neurotip® will be loaded onto a neuropen® (Owen Mumford, USA) which will give a standardized 40 gram force. Sensory testing will be performed from caudad to cephalad (i.e. from blocked to unblocked dermatomes) to identify the first unblocked dermatome.

### **Secondary Outcome**

We will compare the intraoperative supplementation rate between the two groups. This is defined the percentage of women who require additional drugs to control pain during the elective cesarean section in each arm of the trial.

### **Exploratory Outcome**

The following will be abstracted from the medical records:

- Maximum pain Visual analogue scale (VAS) during surgery (as reported by patient, scored from 0-10 in the PACU).
- Incidence of side effects:
  - Nausea (self-reported by patient, yes or no).
  - Vomiting (observed yes or no).
  - Itching (self-reported by patient, yes or no).
- Use and dose of vasopressor phenylephrine (80-160 mcg bolus) and Hartmann's solution (200mls bolus). Indicated to be given if the BP drops greater than 20% below baseline or <100mg Hg systolic.
- Overall patient satisfaction score, (asked and scored from 0-10).
- Motor block at end of the cesarean delivery (measured in the PACU).
- Neonatal Apgar scores.
- Umbilical cord blood gases taken after delivery (arterial and or venous).
- Opioid consumption over 24 hours postoperatively

This is a single center, double blinded, randomized study. Our usual practice for extending epidural analgesia for urgent cesarean sections consists of a mixture of 2% lidocaine, epinephrine, bicarbonate and fentanyl (LEBF) or 3% chloroprocaine. The

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local anesthetic mixture used is dependent on the anesthesiologist's preference. LBEF tends to be used more frequently than chloroprocaine in our unit (estimated 2:1 ratio) Both drugs provide a rapid onset of surgical anesthesia with little need for intraoperative analgesic supplementation.

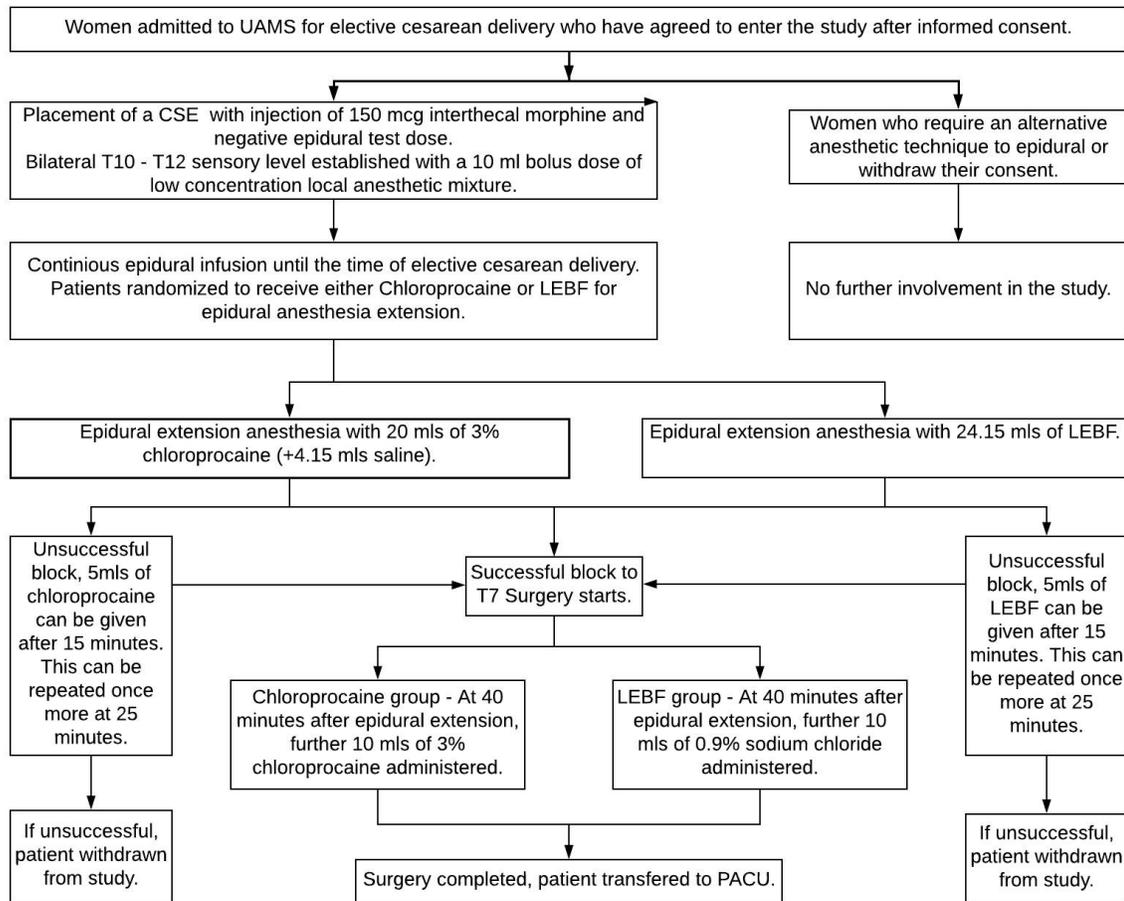
The aim of this study is to compare the speed of onset and anesthetic quality of our two current clinical dosing regimens (LEBF, and a solution of 3% Chloroprocaine) in elective cesarean delivery. Both 2% lidocaine and 3% chloroprocaine are licensed and commonly used in epidural catheters for cesarean delivery. The results of this study should also be applicable to epidural anesthesia in the setting of urgent cesarean deliveries.

Due to the complexities of performing a research study in the setting of an urgent cesarean delivery, we propose testing our hypothesis in patients scheduled for elective cesarean delivery. As such we will be deviating from our standard care, which normally involves spinal, epidural or combined spinal-epidural (CSE) performed in the operating room directly before cesarean delivery. Instead a CSE will be inserted preoperatively in women shortly before their elective cesarean section (usually 1- 2 hours before surgery). This will allow us to closely replicate the conditions involved in extending an epidural that is used for analgesia in laboring women to surgical anesthesia for unexpected cesarean delivery.

The epidural infusion will be commenced with our standardized local anesthetic mixture (0.0625% bupivacaine with 2mcg/ml fentanyl) through an automated infusion pump. This is normally used to provide pain relief in laboring women. This epidural infusion pump will continue until the scheduled time of cesarean delivery. The woman will then be transferred to the operating room and the epidural will be extended/topped-up with either chloroprocaine or LBEF (according to randomized group assignment) so as to assess the onset time of anesthesia for cesarean delivery. Both local anesthetic mixtures (LBEF and chloroprocaine) are commonly used in other hospitals within the region for elective and emergency cesarean delivery. We almost exclusively use these two mixtures in our unit for women who require unscheduled cesarean delivery if they have already had an epidural placed. For elective cesarean delivery our normal practice involves either spinal or CSE anesthesia, epidural anesthesia is more likely to be used for select cases dependent on clinical condition.

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## Study Flow Chart



## Study Design and Procedures

### Screening/Baseline Phase

The anesthesiologists performing the pre-operative evaluation will alert a member of the study team if the patient meets the inclusion criteria for the study. Following informed consent, we will obtain demographic and clinical information including, but not limited to, height, weight, age, current medications, medical diagnoses, and history of anesthesia complications. Standard non-invasive vital signs (heart rate, blood pressure, respiratory rate, and temperature) will be obtained from the pre-operative work up.

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### **Pre-operative Phase**

Patients who have been enrolled into the study will have a combined spinal-epidural (CSE) inserted in the patient's room on admission to the Labor & Delivery Suite (L&D) shortly before (usually 1 -2 hours) their elective cesarean section. Patients who are not enrolled in the study would normally receive either a spinal or CSE in the operating room at the time of their surgery. Dosing and monitoring will be the same as for any patient who requires a CSE for labor analgesia or cesarean delivery.

To proceed with the next phase of the study (see below), the subject will require a functioning epidural. This will be assessed by the anesthesiologist after insertion of the CSE by confirming a negative test dose and the establishment of a bilateral T10 – T12 sensory block. This is standard practice.

### **Intra-operative Phase**

The patient will be transferred from her room (where the CSE was inserted) to the operating room according to her scheduled time of cesarean delivery. The epidural pump will be discontinued and anesthesia care will be conducted in the same manner as all cesarean deliveries under epidural extension anesthesia. The anesthesiologist will confirm that no blood or CSF can be aspirated from the epidural catheter before the administration of the test dose and study solution.

Motor block of the lower extremities will be evaluated using the Bromage scale (1–4; 1, no block; 4, complete motor block). The motor block will be assessed on at least three occasions:

1. Before administering the epidural extension anesthesia
2. When the sensory level reaches the T7 dermatome
3. Postoperatively on admission to PACU

Sensory block will be tested (using a standard procedure) at the end of the epidural loading dose. Loss of touch sensation will be measured using a neurotip® (Owen Mumford, USA) until a sensory bilateral block to the T7 dermatomal level has been reached. The T7 level will be marked bilaterally with a washable marker pen to guarantee precision of the primary end point. A blunt plastic neurotip® will be loaded onto a neuroopen® (Owen Mumford, USA) which will give a standardized 40 gram force. Sensory testing will be performed from caudad to cephalad (i.e. from blocked to unblocked dermatomes) to identify the first unblocked dermatome.

To identify the level where the sensation of touch is first appreciated, the investigator will ask the question: "Tell me when you feel something touch your skin." Both the motor and sensory block evaluations are part of the standard clinical care of patients receiving epidural anesthesia.

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The study solution will be given in three phases:

1. Test Dose
  - 3 mls given initially from the 30-ml syringe labelled: Epidural Study (Induction 1)
2. Induction
  - The remaining volume from the 30-ml syringe labelled: Epidural Study (Induction 1)
  - Epidural Study (Induction 2) syringe may be used if required to further extend the epidural block (as per instructions below)
3. Maintenance
  - A 10-ml syringe labelled Epidural Study (Maintenance) given at 40 minutes after the test dose

Participants in the study will be randomized to receive one of the two study solutions as described above. These solutions in syringes will be prepared by an un-blinded anesthesiologist in the adjacent operating room prior to the epidural top-up. The patient's initials and study number will be displayed on each syringe. The un-blinded anesthesiologist will have no other role in the patient's care other than the preparation of the study solution and replacing the term "study solution" within the patients' medical record, to the actual drugs that were given. In the event of an emergency situation blinding would be broken and the treating anesthesiologist would be informed of what study solution was given.

A second anesthesiologist, blind to the choice of local anesthetic will manage the clinical care of the patient from the beginning of the study (insertion of the epidural) and will administer the epidural study solution. There will be no difference in this clinician's care of the subject than if she were not enrolled in the study. They will assess the onset of anesthesia and manage all aspects of the subject's clinical care including the documentation of the "study solution", timing, and clinical effects of the study medication. The speed of onset will be assessed from the end of epidural top up. This will be defined as time zero and the start of anesthesia. The primary outcome will be the time taken to lose touch sensation from a neurotip/pen device at the thoracic dermatome level 7 (T7). See below for a description of this assessment.

The primary outcome will be documented on a separate data collection tool (which the un-blinded anesthesiologist will not have access to). The blinded anesthesiologist will continue to manage all aspects of the subject's clinical care until completion (PACU discharge). If required intra-operative analgesia will be offered in the form of further epidural top-up, intravenous fentanyl, ketamine, nitrous oxide or replacement of

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neuraxial anesthesia/conversion into general anesthesia at the anesthesiologist's discretion. These are all commonly used medications that provide pain relief during cesarean sections in the event of breakthrough pain. The choice of which drug to use is at the discretion of the anesthesiologist. This information will be abstracted from medical records.

### **Intra-operative Monitoring**

As with all cesarean sections full monitoring in the operating room will be applied and will be the same whether the participant is in the study or not.

### **Concurrent Medication**

Subjects enrolled in the study will be treated as per normal practice for elective cesarean section. If a general anesthetic must be instituted, the subject's participation in the study will be stopped.

### **Assessment of Primary Efficacy Parameters**

Assessment will be made of the sensory level after the epidural loading/induction dose. This will give an indication of the suitability of surgical anesthesia before proceeding with cesarean section. This will be assessed by the blinded clinical anesthesiologist with a Neurotip™ device, 2 minutes after the completion of the epidural top-up and then continuously if possible or at intervals of approximately 1 minute until a T7 level is acquired to touch sensation. Motor function will be assessed using the Modified Bromage Score. This is standard clinical monitoring, except for the fact that the sensory level will be assessed continuously / approximately every one minute as opposed to the ad hoc assessments which are normally done.

### **Epidural Study Solutions**

The solutions and their administration procedures are identical to those used outside this research and are almost exclusively used for epidural top up anesthesia for non-scheduled cesarean delivery. All patients enrolled will randomly receive one of the two study solutions exactly prescribed as below which is our routine practice.

### **Epidural Study Solution 1**

#### **Test Dose and Induction**

Twenty (20) mLs of Chloroprocaine 3% (Nesacaine – Fresenius Kabi), will be drawn up into a 30-ml syringe from 1 x 20-ml single dose vial of 3% Chloroprocaine. 4 mls of 0.9% sodium chloride will be added to the syringe. Thus the total volume in the syringe will be 24 mls. 3 mls of this solution will be initially administered through the epidural.

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This is the test dose. After three minutes the anesthesiologist will assess the patient for any signs of accidental intrathecal or vascular administration. If there are no signs of accidental wrong route administration then the remaining volume of solution will be given via the epidural catheter over approximately two minutes. This will be the induction dose. The total volume that will be administered to the patient at this stage will be 24 mls.

Ten (10) mls of 3% Chloroprocaine will be drawn up in a 20-ml syringe. This solution will be given if the initial induction dose is not effective. If a bilateral block to touch stimulus at the T7 dermatome level has not been achieved within 15 minutes after the end of the induction dose, then a further 5mls of study solution will be given. If after 25 minutes (total elapsed time after giving induction dose), a sensory block to T7 has not been achieved then a further 5 mls of study solution can be given. If at 35 minutes (after induction dose) the sensory block has not reached T7, then the subject will be withdrawn from the study and the anesthesiologist can induce anesthesia in whichever way they think is best. At this point the anesthesiologist will also break blinding. Therefore, the total volume of local anesthesia that can be given to the patient at this stage is 34 mls (24 mls induction dose + a further 5 or 10 mls if the initial induction dose is not effective).

### Maintenance

Ten (10) mls of Chloroprocaine 3% will also be drawn up in a separate 10 ml syringe. This solution will be administered once only over 3 – 5 minutes, 40 minutes after the completion of the induction dose.

## **Epidural Study Solution 2**

### Test Dose and Induction

Twenty (20) mls of Lidocaine 2% HCL (Xylocaine – Fresenius Kabi), which will be drawn up into a 30 ml syringe from 4 x 5ml ampoules of 2% Lidocaine. The following additives will be added:

1. 0.15 ml of 1:1000 epinephrine
2. 2 mls of 50 mcg/ml of fentanyl
3. 2 mls of 8.4% sodium bicarbonate

Thus the total volume in the syringe will be 24.15 mls. At the start of epidural extension anesthesia a 3 mls test dose will be administered through the epidural (as previously described above). After three minutes, if there are no signs of accidental spinal block or intravascular administration then the remaining volume of study solution will be administered over approximately two minutes. This is the induction dose. The total volume that will be administered to the patient at this stage will be 24.15 mls.

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Ten (10) mls of 2% Lidocaine (with the addition of 0.1 ml of 1:1000 epinephrine) will be drawn up in a 20 ml syringe. This solution will be given if the initial induction dose is not effective. If a bilateral block to touch stimulus at the T7 dermatome level has not been achieved 15 minutes after the end of the epidural top up, then a further 5mls of study solution will be given. At the 25 minute mark (total elapsed time after giving induction dose) a further 5 mls of study solution can be given in an attempt to achieve a sensory block to T7. If at 35 minutes (after induction dose) the sensory block has not reached T7, then the subject will be withdrawn from the study and the anesthesiologist can induce anesthesia in whichever way they think is best. At this point the anesthesiologist will break blinding. Therefore, the total volume of local anesthesia that can be given to the patient at this stage is 34.15 mls (24.15 mls induction dose + a further 5 or 10 mls if the initial induction dose is not effective).

### Maintenance

Ten (10) mls of 0.9% sodium chloride will also be drawn up in a separate 10ml syringe. This solution will be administered once only over 3 – 5 minutes, 40 minutes after the completion of the induction dose.

This is our usual practice except for the following:

- we are being very precise in regards to documentation of time
- monitoring the sensory block continuously or approximately every one minute(as opposed to every few minutes)
- the addition of saline to study solution 1, this is to allow equal volumes of local anesthetic solutions and maintain blinding

### Post-operative Phase

Participants will be admitted to the PACU after completion of the operation. Care will be as per the standard of care for all elective cesarean deliveries. Pain scores, motor and sensory block assessments, and cumulative opioid usage over the first 24 hours postoperatively, will be abstracted from the medical records of these subjects after discharge.

Before discharge from the PACU, the un-blinded anesthesiologist would access the patient's medical record and replace the charted "study solution" with the actual drugs administered before closing the anesthetic record.

### **Study Population**

All subjects scheduled for elective cesarean delivery will be screened for recruitment when admitted to UAMS labor and delivery unit. A member of the research team will

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approach the subject after completion of the anesthetic pre assessment which is a standard of care.

### **Inclusion Criteria**

Any patient requiring an elective cesarean section at UAMS labor and delivery unit who is:

- $\geq 18$  years of age for the mother
- Singleton pregnancy
- Gestation  $> 36$  weeks
- ASA class II
- Provides written consent
- Infant of mother

### **Exclusion Criteria**

- Patient refusal
- Non-elective or urgent/emergent cesarean sections
- ASA class III or above
- Unable to understand English
- Significant back surgery or scoliosis
- Lethal fetal abnormality or likely to affect APGAR scores
- Known fetal abnormality
- Weight  $> 120$  kg
- Height  $< 150$  cm
- Allergy to local anesthetics

### **Accrual Goal**

A total of 70 mother-infant dyads requiring an elective cesarean section at UAMS labor and delivery unit will be enrolled into the study.

### **Recruitment Plan**

Potential subjects will be offered participation in the study after admission into the Labor and Delivery unit. All potential subjects will be informed of the study by a member of the study team after the anesthetic pre-operative consultation. The informed consent/HIPAA discussion will take place prior to any pre-operative medications being administered and the potential subject will be allowed as much time as necessary to consider participating in the study.

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## **Risks and Benefits**

The benefits and risks to the study participants overall will be the same as all patients presenting to L&D for elective cesarean delivery. That is, whether a patient decides to participate or not in the study, the normal standard of care is neuraxial anesthesia (spinal, epidural or combined spinal-epidural) for cesarean delivery as opposed to general anesthesia. Below is a brief summary of the three main neuraxial anesthesia techniques; spinal, epidural and CSE.

### *Spinal Anesthesia*

The majority of elective cesarean delivery is performed under spinal anesthesia. The main advantage of spinal anesthesia is its fast onset, good quality anesthesia and it is a relatively simple anesthetic technique. The main disadvantage is that spinal anesthesia has a limited duration of action (under two hours) and intraoperative pain will require supplementation with intravenous drugs or conversion to general anesthesia

### *CSE and epidural anesthesia*

These techniques will be considered together as they are similar. We rarely use epidural anesthesia for elective cesarean delivery, mainly because its onset of action is much slower than spinal anesthesia. Epidural anesthesia is routinely used for nonscheduled cesarean delivery, where laboring patients will likely already have an epidural in place. The epidural is then “toped up” allowing the conversion of labor analgesia to surgical anesthesia. Hence the main advantage of epidural anesthesia is the ability to extend analgesia or anesthesia for as long as required. This also allows the administration of further local anesthetic solution through the epidural to treat any episodes of intraoperative pain without having to convert to general anesthesia.

A CSE technique combines the advantages of spinal and epidural anesthesia. Therefore, it is routinely used for elective cesarean delivery (but less than spinal anesthesia). The disadvantage of the CSE technique is that is the most technically challenging of the three anesthetic techniques as it combines both a spinal and an epidural.

### *Risks of CSE and epidural anesthesia*

- The benefits and risk of spinal, epidural, CSE and general anesthesia are routinely discussed with the patient as part of the anesthetic pre-assessment and informed consent as a standard of care. The subject will be exposed to very similar risks if they decided to be part of this study or not as they will most likely receive neuraxial anesthesia (spinal/epidural/CSE) as opposed to general anesthesia if they decline to be in the study. However, subjects enrolled into this study will all receive CSE anesthesia. The only unique risk to participants in this study due to CSE anesthesia is: Inadvertent intravascular injection. This risk can

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be minimized by aspirating blood through the epidural catheter and administering a 'test dose' of local anesthetic +/- epinephrine.

- Our standard CSE equipment is composed of a spring wound catheter. This greatly reduces the risk of the epidural catheter entering a blood vessel and hence the risk of intravascular administration
- The above interventions are usually enough to minimize the risk of any hazards to intravascular injection that we do not normally include intravascular injection as part of the consent process.

### *Advantages and disadvantages of having a CSE placed early*

As part of this study's protocol, participants will have a CSE placed early. The benefits include having the anesthetic technique placed in the participants room, in a more relaxed environment and in a less rushed manner than in the operating room. The subject can also have their birthing partner to support them during the procedure, which would not be possible if the procedure were to be done in the operating room.

There are also disadvantages of having a CSE placed early. The main disadvantage is likely to be a reduction in the patient's mobility. We expect the CSE to be placed 1- 2 hours before the scheduled cesarean delivery. During this time that the epidural pump is running, the subject is given instructions not to walk. Their options will be to stay on the bed or the chair. Any mobilization (from the bed to the chair or vice versa) will require the assistance of a nurse. A urinary catheter is not required.

Research related risk to study participants include the potential for loss of confidentiality. Measures to protect the confidentiality of study participants will be implemented as described in the Data Handling and Recordkeeping section below.

There will be no direct benefits to the study participants; however, knowledge gained from the study could potentially benefit patients in the future.

### **Study Medication Risks**

#### **Lidocaine with epinephrine and chloroprocaine**

These medications are considered together as they are both local anesthetic drugs that will be administered through the epidural route:

#### **Severe allergic reactions (rare, may affect up to 1 in 1,000 people)**

- Swelling of the face, lips, tongue or throat. This may make it difficult to swallow.
- Severe or sudden swelling of the hands, feet and ankles.
- Difficulty breathing.
- Severe itching of the skin (with raised lumps).

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**Other possible side effects:**

- Numbness where the injection is given. This will go away slowly.

**Common (may affect up to 1 in 10 people)**

- Low blood pressure. (causing dizziness or light-headedness).
- High blood pressure.
- Feeling sick (nausea) or being sick (vomiting).
- Pins and needles.
- Feeling dizzy.
- Slow heart beat.

**Uncommon (may affect up to 1 in 100 people)**

- Ringing in the ears (tinnitus) or being sensitive to sound.
- Difficulty in speaking.
- Numbness of the tongue or around the mouth.
- Fits (seizures).
- Feeling sleepy.
- Shakiness.
- Blurred vision.

**Rare (may affect up to 1 in 1,000 people)**

- Uneven heart beat (arrhythmias).
- Nerve damage that may cause changes in sensation or muscle weakness (neuropathy). This may include peripheral nerve damage.
- A condition called arachnoiditis (inflammation of a membrane that surrounds the spinal cord). The signs include a stinging or burning pain in the lower back or legs and tingling, numbness or weakness in the legs.
- Double vision.
- Slowed or stopped breathing or stopped heart beat.
- Total spinal block

**Possible side effects seen with other local anesthetics which might also be caused by Lidocaine with epinephrine or chloroprocaine include:**

- Damaged nerves which may cause permanent problems.

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### **Side effects to the fetus:**

- Local anesthetics rapidly cross the placenta and when used for epidural, can cause varying degrees of fetal and neonatal toxicity. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.
- It is not known whether these drug are excreted in human milk

### **Sodium Bicarbonate (frequency unknown)**

- Tissue necrosis, ulceration or sloughing has been reported following extravasation at the site of injection.
- Compensatory hyperventilation, paradoxical acidosis in the cerebrospinal fluid, severe hypokalemia, volume overload, pulmonary oedema, shortness of breath, muscle weakness (associated with potassium depletion). Muscle hypertonicity, twitching, hyperirritability and tetany may develop especially in hypocalcaemic patients. Seizures may be exacerbated or precipitated in epileptic patients.
- It is not known whether sodium bicarbonate can cause fetal harm when administered to a pregnant woman or whether it is excreted in human milk

### **Fentanyl**

#### **Very common side effects (affect more than 1 in 10 people) include:**

- muscle stiffness • feeling sick (nausea), or being sick (vomiting)

#### **Common side effects (affect less than 1 in 10 people)**

- feeling agitated • jerky or uncoordinated movements • drowsiness • dizziness • blurred vision, blind spots or haloes around lights (visual disturbances) • a slow or irregular heartbeat • unusually low or high blood pressure • pain along your veins • choking caused by cramping (spasm) of the muscles of your throat • wheezing or difficulty breathing • stopping breathing for a short period of time. If necessary your breathing will be helped by a machine (ventilator). • an itchy rash or redness of the skin • confusion

#### **Uncommon side effects (affect less than 1 in 100 people) include:**

- a feeling of extreme happiness (euphoria) • headache • swelling and clotting along a vein • changes in blood pressure • breathing faster than usual • hiccups • decrease in body temperature or chills • breathing complications Other side effects (frequency not known) include: • a serious allergic reaction (see symptoms above) • convulsions (fits or seizures) • loss of consciousness •

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muscle twitching • stopping of the heart (cardiac arrest) • slow or shallow breathing • itching of the skin

### **Side effects to the fetus**

- In women treated acutely with IV or epidural fentanyl during labor, symptoms of neonatal respiratory or neurological depression were no more frequent than would be expected in infants of untreated mothers
- Fentanyl is excreted into human milk and achieves levels in colostrum which are greater than maternal serum levels. No adverse effects have been reported in nursing infants.

### **Risk Mitigation**

All subjects will be observed in a unit accustomed to treating patients recovering from surgery and anesthesia. Customary clinical care will be provided by the patient's treating physician. No standard treatments will be withheld as a result of participation in the study.

### **Drug Accountability and Subject Compliance**

This study will take place within the UAMS hospital's labor and delivery unit. There will be full drug accountability throughout the study. There will be an accountability log, labels for each ampoule marked especially for the study (Epidural Study). Study drugs will be prepared by one anesthesiologist (un-blinded) and administered by another anesthesiologist (blinded). The dose of study solution in milliliters given to the patient will be documented within anesthetic record by the blinded anesthesiologists. Initially this will be documented only as "study solution" After completion of the study, the un-blinded anesthesiologist will complete the anesthetic record by entering the names of the actual study medications given. Compliance will be confirmed by comparing the medical chart to the accountability logbook.

### **Data Handling and Recordkeeping**

The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study. All study subject material will be assigned a unique identifying code or number. The key to the code will be kept in a locked file cabinet and password protected Principal Investigator's computer in the Principal Investigator's office. Only Nadir Sharawi, MD and Jill Mhyre, MD will have access to the code and information that identifies the subject in this study. At the conclusion of the study, the data will be permanently deidentified. Deidentified study data will be maintained and ultimately destroyed per UAMS policy.

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## **Data Analysis**

The null hypothesis is that chloroprocaine group will have a slower onset time to achieve loss of touch sensation at the T7 dermatome compared to the LEBF group.

The alternative hypothesis is that the chloroprocaine group will have no difference in onset time to achieve loss of touch sensation at the T7 dermatome compared to the LEBF group.

For statistical analysis, the Student's t- test will be used for continuous normally distributed variables and the Mann-Whitney test for nonparametric variables. Linear regression analysis will be used to assess any relationship between the pre top-up parameters and the subsequent speed of onset of the block.

## **Sample Size**

The sample size will be calculated for continuous outcome date for a non-inferiority study. We have assumed that an onset time difference of three minutes is the largest difference that is clinically acceptable, so that a difference of more than three minutes would matter in clinical practice. If there is truly no difference between the LEBF group and the chloroprocaine group, then 62 mother-infant dyads are required to be 90% sure that the lower limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will be above the non-inferiority limit of 3 minutes with a standard deviation of 4 minutes. Therefore 31 patients will be recruited to each arm. Statistical significance will be taken as  $P < 0.05$ . In total, 70 female patients will be recruited to account for any withdrawals.

## **Randomization**

Thirty-five pieces of paper will be printed for each group containing 3% Chloroprocaine or 2% LEBF for a total of 70. Each of the individual piece of paper will then be placed in a sealed envelope. All envelopes will be shuffled and then numbered 1 – 70.

Patients will be assigned a number 1 – 70 as they are enrolled in the study. The envelope will be obtained and opened by an un-blinded anesthesiologist revealing their randomization group. The un-blinded Anesthesiologist will not be involved in the patient's care or data collection. They will prepare the epidural study solution and close the patient's anesthetic record at the end of the study after charting which study solution was administered by the blinded anesthesiologist. They will not be aware of primary outcome result as this will be documented on a separate data collection form. All members of the patient's care team are blinded to the assignment study drug. The un-blinded anesthesiologist will inform the clinical team which drug was used if determined to be clinically necessary.

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### **Withdrawal of Participants**

Subjects will have the right to withdraw from the study at any point in time and have the right to withdraw any accompanying data. The study has been powered to account for a 10% withdrawal rate.

### **Stopping the Study**

Epidural anesthesia will be discontinued if the woman experiences significant pain that is not relieved by the intraoperative analgesic supplementation described above or if the patient is no longer able to continue with epidural anesthesia. At this point the subjects' participation is over. Depending on the clinical scenario, an alternative anesthetic technique will be offered, usually general anesthesia.

### **Ethical Considerations**

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.

The formal consent of each subject, using the IRB-approved consent/HIPAA form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent/HIPAA form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent/HIPAA form must be signed by the subject and the individual obtaining the consent. A copy of the signed consent/HIPAA will be given to the participant, and the informed consent process will be documented in each subject's research record.

### **Dissemination of Data**

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant.

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3. Gaiser, R. R., T. G. Cheek, and B. B. Gutsche. 1994. "Epidural Lidocaine versus 2-Chloroprocaine for Fetal Distress Requiring Urgent Cesarean Section." *International Journal of Obstetric Anesthesia* 3 (4): 208–10.

## Appendices

1. Bromage Score
2. Neonatal Apgar Score
3. Pain Visual Analogue Scale (VAS)